IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Luyten et al.
Appl. No.	:	09/574,819
Filed	:	May 19, 2000
For	:	CARTILAGE-DERIVED MORPHOGENETIC PROTEINS
Examiner	:	Romeo, David S
Group Art Unit	:	1647

SUPPLEMENTAL DECLARATION OF PRIOR INVENTION IN THE UNITED STATES TO OVERCOME CITED PUBLICATION UNDER 37 CFR § 1.131

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

1. This declaration is to establish completion of the invention of this application in the United States at a date prior to 14 April 1994, the date that appears on Storm et al. Nature 368:639-643 (1994), which we understand was cited by the examiner.

2. The persons making this declaration are the named co-inventors.

3. Attached herewith is a true copy (Exhibit A, page 6) of a laboratory notebook page dated prior to April 14, 1994, the date of which has been removed. This page shows that primers corresponding to highly conserved motifs in the mature region of the BMPs were used to amplify and clone DNA from *Xenopus* genomic DNA.

4. Attached herewith is a true copy (Exhibit A, pages 6-7) of laboratory notebook pages dated prior to April 14, 1994, the dates of which have been removed. These pages show that miniprep DNA samples from 48 of the *Xenopus*-derived clones were analyzed by EcoRI restriction digestion. Clones were considered to be positive or weakly positive if they had an insert of the size expected for a BMP-related fragment.

5. Attached herewith is a true copy (Exhibit A, page 8-10) of laboratory notebook pages dated prior to April 14, 1994, the dates of which have been removed. These pages show that thirty six of the positive or weakly positive miniprep DNA preparations were sequenced by the Sanger (dideoxy) chain termination protocol and that 15 clones were determined to be similar to TGFβ.

6. Attached herewith is a true copy reduced in size to 8-1/2 by 11 inches (Exhibit B) of a sequencing autoradiogram dated prior to April 14, 1994, the date of which has been removed. This page contains readable sequence for the complete insert of Sample #3 (132 base pairs flanked by EcoRI sites). The dideoxy-terminated reactions were run in the order A, C, G and T.

7. Attached herewith is a true copy (Exhibit C) of a laboratory notebook page dated prior to April 14, 1994, the date of which has been removed. This page provides the nucleotide sequence of the Sample #3 insert read from the sequencing autoradiogram and recorded in three vertical columns in the middle of the page. The nucleotide codon triplets were translated to the corresponding amino acid sequence which was written adjacent to the nucleotide sequence. This experiment showed that the sequence of Sample #3 was similar to a "TGFβ factor".

8. Referring to Exhibit C, we noted in the heading for Sample #3 in red ink that it was "Like Logan's #21 24 AA, 1 different". Logan's sample #21 refers to the sequence for zebrafish CDMP, which was cloned using the same approach as described above for the *Xenopus* product. The *Xenopus* sequence (written in black ink) shares an amino acid sequence motif WIIAPLEYEAYHCEGVCDFPLRSHLEPTNHA (SEQ ID NO: 24) in common with the zebrafish CDMP except at one position (underlined in the above motif and the middle column, fourth amino acid from the bottom of Exhibit C). *Xenopus* has an E at this position (which is GDF-6 of Storm et al.) but zebrafish has a D (which is probably GDF-7 of Storm et al.). The amino acid sequence positions were in the products obtained by PCR. It was understood from these results that the *Xenopus* and zebrafish sequences are members of a new class, which we designated CDMP.

9. Referring to Declaration of Prior Invention in the United States to Overcome Cited Publication Under 37 CFR § 1.131, signed July 2004, which is hereby incorporated by reference, and Declaration Under 37 CFR § 1.131, signed August 1999, which is hereby incorporated by reference, it can be seen that the bovine sequence shares the amino acid sequence motif of SEQ ID NO: 24 in common with the *Xenopus* CDMP. The amino acid sequence residues were identical at every position in the products obtained by PCR using the same primers corresponding to highly conserved motifs in the mature region of the BMPs. It was understood from these results that the *Xenopus* and bovine sequences are members of a new CDMP subclass, which we designated CDMP-2 and which is GDF-6 of Storm et al.

10. From these documents it can be seen that we, the inventors, had possession of the genus of molecules within the TGF-β family defined by the common amino acid sequence motif of SEQ ID NO: 24 at a date prior to April 14, 1994.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application and any patent issued thereon.

Respectfully submitted,

Dated: Nov 30 2005

By: _____
Frank P. Luyten, M.D.

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Filed : **May 19, 2000**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application and any patent issued thereon.

Respectfully submitted,

Dated: November 30, 2005

By: Malcolm Moos Jr, MD PhD
Malcolm Moos, Jr., M.D., Ph.D.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application and any patent issued thereon.

Respectfully submitted,

Dated: 11/30/05

By: _____
Steven C. Chang, M.D.

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